limitations of the dependent claims from which they were previously dependent. Claims 17 and 96 have been amended to indicate that hybridization is under stringent conditions. The second claim numbered 91 has been renumbered as claim 97. Claims 9, 16, 17, 19-22, 46, 59-66, 77-80, 85, 87-92, and 95-97 are currently pending. Applicants respectfully assert that this amendment and response place the claims in better condition for allowance. The amendment raises no new issues. Thus, Applicants request that this response be entered. Applicants respectfully request favorable reconsideration and withdrawal of all pending rejections based on these amendments and the following remarks.

Applicants bring to the Examiner's attention the following co-pending applications: U.S. Patent Application Serial Nos. 09/414,295 and 60/146,580 (filed as a non-provisional utility application on July 27, 2000) and PCT Application Nos. PCT/US 00/20532 and PCT/US 00/20544, both filed on July 28, 2000, at the U.S. Receiving Office.

Rejection Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner rejected claims 1-23, 30-39, 45, 46, 59-66, 77-80, 85, 87-92, 95 and 96 as unpatentable over claims 1-39, 45 and 46 of copending Application No. 08/822,774. Office Action at Page 2, Item No. 3. The Examiner alleged that because Applicants had not argued this rejection in the previous response, Applicants would "not

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be allowed to argue points that could have been argued at this time." Id.

Applicants note that since copending Application No. 08/822,774 had not issued at that time, thus this rejection is provisional. Consequently, Applicants assert that there is no obligation to argue a provisional rejection. Applicants further assert that they retain the right to argue the merits of this rejection at a later date. The Examiner acknowledged this during the interview, as indicated in the Examiner's Interview Summary.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-23, 30-39, 45, 46, 59-66, 77-80, 85, 87-92, 95, and 96 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action at Page 2, Item No. 4. Specifically, the Examiner alleged that the rejected claims are indefinite "in the recitation of 'polymerase enhancing factor' (PEF) in view of the definition of PEF." *Id.*, Item 4A.

Applicants respectfully traverse the rejection. Applicants have canceled claims 1-8, 10-15, 18, 23, 30-39, and 45 without prejudice or disclaimer. Thus, the rejection of these claims is moot. Applicants do not concede that the definition of PEF in the specification is indefinite. During the Examiner interview of May 19, 2000, Applicants' representative pointed out that the rejected claims do not recite the terms "PEF" or

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"polymerase enhancing factor." The Examiner stated that he would withdraw this basis for rejecting the claims.

The Examiner also rejected claims 95 and 96 because they allegedly define a protein in terms of hybridization function. *Id.*, Item 4B. Applicants respectfully traverse this rejection. Claims 95 and 96 recite at least two limitations. First, these claims are directed to compositions of matter "comprising a polymerase enhancing protein," that is a protein with polymerase enhancing activity. Second, the polymerase enhancing protein is encoded by an isolated or purified DNA sequence that hybridizes to the complement of an identified nucleotide sequence.

Thus, proteins that lack polymerase enhancing activity are not within the literal scope of the claim. Further, proteins encoded by a DNA sequence that does not hybridize to the complement of the nucleotide sequences, as recited in claims 95 and 96, are likewise beyond the literal scope of those claims. Applicants respectfully assert, therefore, that those claims do not merely define a protein in terms of nucleic acid hybridization as alleged by the Examiner. Further, Applicants assert that one skilled in the art would understand the scope of those claims. Consequently, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Finally, claims 1-23, 30-39, 45, 46, 59-66, 77-80, 85, 87-92, 95, and 96 were rejected as allegedly being indefinite because the claims recite the terms "analogs thereof," "sequences hybridizable thereto," "degenerate variants thereof," and "wholly

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or partially synthetic protein." Id. at Item 4C.

Applicants respectfully traverse this rejection. Applicants have canceled claims 1-8, 10-15, 18, 23, 30-39, and 45 without prejudice or disclaimer. Thus, the rejection of these claims is moot. Further, none of the pending claims recite the term "degenerate variants thereof" or any related term. Therefore, this basis for the rejection is improper.

It is incumbent on the Examiner to establish that the person of skill in the relevant art, when reading the claims in light of the specification, would not have been able to determine with a reasonable degree of precision the subject matter circumscribed by the claims. *Ex parte Wu*, 10 U.S.P.Q.2d 2031, 2033 (Bd. Pat. App. & Int. 1989). Further, if the claims, read in light of the specification, reasonably apprise the person of skill in the relevant art of the scope of the invention and the language is as precise as the subject matter permits, no more is required. *North American Vaccine, Inc. v. American Cyanamid Co.*, 28 U.S.P.Q.2d 1333, 1339 (Fed. Cir. 1993), *cert. denied*, 114 S. Ct. 1645 (1994).

Applicants assert that the skilled artisan would readily understand that the term "wholly or partially synthetic protein," means a protein generated, at least in part, by synthetic processes including chemical or biochemical synthesis, rather than a protein isolated from nature. *See, e.g.,* Specification at pages 16 and 17. For example, claim 1 recites in part "a wholly or partially synthetic protein having the same amino acid sequence as said naturally-occurring protein or analogs thereof possessing polymerase

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enhancing activity." Thus, Applicants respectfully assert that this term is not indefinite and that the person of skill in the relevant art would understand with a reasonable degree of precision the subject matter circumscribed by these claims.

Applicants likewise assert that the term "analogs thereof" is understood by the skilled artisan reading the claims in light of the specification. That term is not used in a vacuum. Rather the claim language itself and the specification provides the proper context for interpreting the term. *See, e.g.,* Specification at page 18, lines 3-5. For example, claim 9 further recites "... the same amino acid sequence as said naturally occurring protein or analogs thereof possessing polymerase enhancing activity." Thus, the skilled artisan, reading claim 9 as a whole, would understand that "analogs thereof" must have amino acid sequences that are similar to the naturally occurring protein and must also possess polymerase enhancing activity. Further, the skilled artisan would understand, in light of the specification, that an analog of a protein possessing polymerase enhancing activity may be generated by mutating, modifying, truncating, or otherwise changing the protein's amino acid sequence only to the extent that the analog retains polymerase enhancing activity. *Id.*

In another example, claim 80 recites "wherein the P45 protein is an analog P45 protein." The specification states that a P45 analog protein may be created by introducing a mutation into the P45 coding region, but that the P45 analog protein substantially retains one or more specific polymerase enhancing activities.

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Specification at page 47, lines 20-26. Thus, Applicants assert that the skilled artisan would readily understand the scope of the claimed subject matter when the claims are read in light of the specification.

Applicants also assert that the term analog is as precise as reasonably possible under the circumstances. To identify the boundary between the two hypothetical extremes, as suggested by the Examiner, would require that each and every position within a protein sequence be varied through an infinite range of substitutions, insertions, and deletions, to identify those that retain polymerase enhancing activity. This degree of precision is beyond what is required by law. Applicants assert that the skilled artisan, reading the claims in light of the specification, would reasonably comprehend the scope and meaning of the claim term "analogs."

Applicants note that the term "sequences hybridizable thereto" does not appear in the pending claims. The term "that hybridizes to the complement of the nucleotide sequence" appears in claims 17, 95, and 96. Applicants assert that the skilled artisan would comprehend the scope and meaning of this term. Without acquiescing to the Examiner's rejection, and solely to expedite prosecution, claims 17 and 96 have been amended to add the term "under stringent conditions." Claims 17, 95, and 96 now recite that hybridization occurs under stringent conditions. The specification provides an example of stringent conditions as overnight hybridization at 42° C and washing four times with 0.1 x SSC, 0.1% SDS at 60° C. Specification at page 31, lines 31-33.

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Additionally, claims 17, 95 and 96 also require that the claimed composition of matter comprise polymerase enhancing activity. Applicants respectfully assert, therefore, that the skilled artisan would understand the meaning and the scope of these claims.

For these reasons, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §112, First Paragraph-Enablement

The Examiner rejected claims 1-23, 30-39, 45, 46, 59-66, 77-80, 85, 87-92, 95 and 96 under 35 U.S.C. §112, first paragraph, alleging that the specification is not enabling because it would allegedly require undue experimentation to practice the invention as claimed. Office Action at pages 4 and 5, Item No. 6. *Id*. Applicants respectfully traverse this rejection.

To be enabling, a specification must teach the skilled artisan how to make and use the claimed invention without undue experimentation. *In re Moore*, 169 U.S.P.Q. 236, 239 (C.C.P.A. 1971). The test for undue experimentation, however, is a matter of degree of difficulty, not merely a quantitative inquiry. *PPG Industries Inc. v. Guardian Industries Corp.,* 37 U.S.P.Q. 2d 1619, 1623 (Fed. Cir. 1996). A considerable amount of experimentation is permissible, provided that it is merely routine. *Id. citing Ex parte Jackson,* 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982); *see also Amgen, Inc. v. Chugai Pharmaceutical Co.,* 18 U.S.P.Q. 2d 1016, 1026 (Fed. Cir. 1991). A considerable

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amount of experimentation is also permissible if the specification provides a reasonable amount of guidance regarding how the experimentation should proceed to practice the invention. *PPG Industries,* 37 U.S.P.Q. 2d at 1623.

Claims 1-8, 10-15, 18, 23, 30-39, and 45 have been canceled without prejudice or disclaimer. Thus, the rejection of these claims is moot.

Applicants assert that the Examiner has failed to establish that the specification would not enable one skilled in the art to make and use a composition comprising polymerase enhancing activity or a polymerase enhancing protein obtained from an archaeal source. Applicants' specification provides detailed guidance for obtaining polymerase enhancing compositions or polymerase enhancing proteins, such as PEF, from archaeal samples, using procedures that are well known to the skilled artisan such as column chromatography, gel electrophoresis and analogous techniques.

The specification teaches that PEF obtained from *Pyrococcus furiosus* enhances the polymerase activity of a variety of archaeal DNA polymerases in PCR reactions. Specification at page 14, line 17 through page 15, line 17, and Figures 33-36. This teaching indicates that at least within the archaebacteria the polymerase enhancing factors may be interchangeable. The specification also teaches methods for identifying related proteins by computer-based analyses of multiple databases using the BlastX program and methods for screening cellular extracts for polymerase enhancing activity. *Id.* at Examples 1 and 9.

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The specification also teaches methods of purifying PEF complexes from samples exhibiting PCR enhancing activity. *Id.* at Example 2. Methods for characterizing partially-purified PEF are also provided. *Id.* at Examples 3 and 4. The amino acid and nucleotide sequences for the P45 and P50 subunits of the *Pfu* PEF complex are provided and related proteins are identified by sequence homology. *Id.* at Examples 5-9. The specification also teaches methods for anti-PEF antibody preparation and antibody-based screening. *Id.* at Example 10.

Applicants assert that persons skilled in the art, reading the specification as a whole, would readily comprehend the teaching of methods for obtaining composition comprising polymerase enhancing activity or polymerase enhancing proteins, such as PEF from archaebacterial sources and that only routine, not undue experimentation need be applied. The person of ordinary skill, based on the teachings of the specification, would also have a reasonable expectation that analogous techniques could be used to obtain compositions comprising polymerase enhancing activity, polymerase enhancing proteins, and the like from a variety of archaebacteria.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §112, first paragraph, rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-23, 30-39, 45, 46, 59-66, 77-80, 85, 87-92, 95,

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and 96, under 35 U.S.C. §103 (a) as allegedly being unpatentable over Sorge et al., U.S. Patent No. 5,556,772 ("Sorge") for reasons of record. Office Action at page 5, Item No. 7. The Examiner further alleges that the previous Office Action explicitly pointed out where factors that enhance polymerase activity are discussed by Sorge. *Id.* at pages 5 and 6, Item No. 8. In the previous Office Action, the Examiner alleged that Sorge disclosed "references teaching the isolation of the *Pyrococcus furiosus* DNA polymerase (Sorge col. 6, line 15)." Office Action mailed March 2, 1999, at page 6, Item No. 7.

Applicants respectfully traverse this rejection. First, claims 1-8, 10-15, 18, 23, 30-39, and 45 have been canceled without prejudice or disclaimer. Thus, the rejection of these claims is moot.

Second, the line in Sorge identified by the Examiner cites a Lundberg article entitled "High-fidelity amplification using a thermostable polymerase isolated from *Pyrococcus furiosus*" *Gene* 108:1-6 (1991). *See* Sorge, col. 6, lines 13-17. (A copy of Lundberg is enclosed for the Examiner's convenience)

Contrary to the Examiner's contention that Lundberg "discusses factors that enhance polymerase activity," Lundberg states that the *Pfu* DNA polymerase that they used "was purified to greater that 99% homogeneity as visualized by polyacrylamide-gel electrophoresis." *See* Office Action mailed March 2, 1999 at pages 6 and 7, Item No. 7; Lundberg, page 2, first column. Lundberg then examines the enzymatic activity

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of highly purified *Pfu* DNA polymerase. Applicants acknowledge that Lundberg discusses the enzymatic activity a highly purified polymerase. Lundberg, however, neither teaches nor would have suggested factors that enhance polymerase activity.

The Examiner stated during the interview that Sorge suggests combining two or more polymerases to obtain enhanced polymerase activity. Applicants respectfully assert that "polymerase enhancing factor," compositions comprising polymerase enhancing activity," and "polymerase enhancing protein" enhance polymerase activity, but do not encompass "polymerase" or "high-fidelity polymerase." Thus, Applicants do not claim such a polymerase. Rather, Applicants claim compositions of matter, i.e., proteins, protein complexes, partially purified cell extracts, and mixtures containing one or more proteins, that "enhance the activity of polymerases." *See, e.g.,* specification at page 6, lines 20-21.

For these reasons, Sorge would not have suggested the claimed invention. Thus, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the preceding remarks, Applicants respectfully assert that pending claims 9, 16, 17, 19-22, 46, 59-66, 77-80, 85, 87-92, and 95-97 are in condition for allowance. In the event that the Examiner does not find the claims allowable, Applicants request that the Examiner contact the undersigned at (650) 849-6656 to set

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up an interview.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: August 16, 2000

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